

Spontaneous Abortion and Exposure during
Pregnancy to the Herbicide 2,4,5-T

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DURING PREGNANCY TO THE HERBICIDE 2,4,5-T

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DURING PREGNANCY TO THE HERBICIDE 2,4,5-T

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ABSTRACT

The purpose of this study was to identify locations in the United States where community exposure to the phenoxy herbicide 2,4,5 Tri-chlorophenoxyacetic acid (2,4,5T) could be examined in relation to the risk of spontaneous abortion and other adverse pregnancy outcomes. Prior ecologic studies evaluating the reproductive consequences of exposure to 2,4,5T have produced equivocal results. In this report, we consider what research strategies and what populations may be used to generate evidence that can be more readily interpreted.

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I. Background

In February 1979, the Environmental Protection Agency issued the results of an investigation into the relation of aerial applications of the herbicide 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) in a forested area of Oregon and spontaneous abortion in populations residing nearby (U.S. Environmental Protection Agency, 1979). In the report, it was concluded that exposure to 2,4,5-T in connection with forest management increased the risk of spontaneous abortions in the population exposed. This conclusion was based on:

- (1) A comparison of spontaneous abortion ratios (abortions: livebirths) in the study area compared with ratios in two nonforested areas of Oregon.
- (2) A comparison of the frequency of abortions occurring in months relating to herbicide use with that occurring in months unassociated with herbicide use.
- (3) A correlation of monthly amounts of herbicide applied and monthly spontaneous abortion ratios.

The report received considerable attention, partly because human evidence on this question is scant and partly because the results appeared to concur with evidence from animal studies showing an increased rate of fetal loss in association with exposure to 2,4,5-T and to its contaminant 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Nevertheless, the conclusions may have been unwarranted.

Unfortunately, the Oregon study had been conducted under considerable time pressure in order to serve as a guide for regulatory action in the next spraying season; subsequent evaluation of the data and the analysis have pointed up several serious limitations.

The following aspects are of primary importance in evaluating this study:

1. Herbicide application data had been obtained for only a portion (25%) of the study area and the assumption was made that the pattern of use (in terms of amounts and timing) would be "similar" in the rest of the study area.
2. Ascertainment of spontaneous abortions was confined to abortions noted in hospital records. Since in this region, most care is sought through private physicians, the use of hospital records will seriously underestimate the number of abortions.

3. The ecological nature of the study, that is, the absence of data to confirm that couples had indeed been at their usual residence during pregnancies, would prohibit, in any case, strong conclusions regarding the relationships of 2,4,5T exposure to abortion. At best, the results could only be taken to suggest a relationship which would need to be confirmed in a study carried out at the individual level.

Not only were there significant limits to what could be learned from this study about the risk to human reproduction in connection with the use of 2,4,5T in forest management, but clearly nothing could be inferred about possible risks associated with other types of uses of 2,4,5T, such as applications to rangelands, rice, or orchards.

Accordingly, this feasibility study was undertaken to determine whether and how the relation of 2,4,5-T to human reproduction could be examined at the individual level of analysis.

II. Objectives of the Study

The objectives of the feasibility study were:

1. To identify areas with: (a) a potentially high level of exposure to 2,4,5T; (b) available documentation of herbicide use; and (c) an exposed population of sufficient size to provide a sample of pregnancies large enough for studying the relation of 2,4,5T to the risk of spontaneous abortion.
2. To outline preliminary study designs for conducting research on this relationship in the location(s) so identified.

It was understood that the work would entail both a review of the original study area (Alsea, Oregon) as a site for an expanded investigation, as well as assessment of other locations which might serve as alternative or concurrent sites for testing the hypothesis that exposure to 2,4,5T under typical conditions of use is associated with an increased risk of spontaneous abortion and other adverse reproductive events. Thus, the first task was to assess the potential for exposure associated with different types of use of this phenoxy herbicide in different areas of the country.

III. Evaluation of Uses of 2,4,5T: Potential for Human Exposure

The herbicide 2,4,5T and related phenoxies are defoliant used in brush and weed control. The principal applications are on: forests; crops, such as rice, wheat and fruits; brush along roadsides and power line right-of-way; private pasturelands and gardens; and rangelands. Of the various types of use rice and timber cultivation seem to hold the greatest promise for studying the possible effects of 2,4,5-T on the reproductive health of exposed populations. The limitations associated with the other uses are summarized below.

A. Wheat Crops

The phenoxy chiefly used is 2,4-dichlorophenoxyacetic acid (2,4-D) which is not contaminated with dioxin. The application rate, though similar to the rate associated with other agricultural uses, is half that associated with forest use (0.5-1.5 pounds (lbs) per acre versus 2-3 lbs per acre); since wheat growing areas are sparsely settled and wheat farming is highly mechanized, the size of the population likely to be exposed is very small; it is not certain that records pertaining to herbicide applications on wheat are routinely kept.

B. Fruit Orchards

2,4,5-T has not been used often on fruit, although 2-2,4,5-trichlorophenoxy propionic acid (2,4,5-TP) (Silvex) is used to some extent; since the herbicide is applied using air blast sprayers mounted on trucks, it may be less likely to drift onto nearby settlements than when applied aerially; farm workers are typically migrants and likely to be difficult to trace.

C. Roadside and Right-of-Ways

This use of herbicides is extensive, and the application rate is high (4-10 lbs per acre); however, depending upon the target vegetation, compounds other than 2,4,5-T may be used. Applications are tractor-managed, and considered to have a limited potential for drift. Roadside applications are carried out by county, state, corporate and federal crews, and the existence and availability of records vary greatly depending on the site.

D. Rangeland

The average application rate on range is from 0.5-2 lbs per acre, and in some states is reputed to be as high as 10 lbs per acre. By definition, rangeland is very sparsely settled; thus it is unlikely that large numbers of people are exposed.

E. Pastureland and Home and Garden Uses

It has been argued that applications of this kind may carry the highest exposure. There are, however, no records of such applications and it seems unlikely that accurate data regarding the timing and use of herbicides in the past could be obtained from personal interview. The uses which seem feasible to explore and likely to yield relevant data are the aerial applications of 2,4,5-T in connection with timber production and rice cultivation. Brief descriptions of the conditions and function of the herbicide use in each of these settings, and a summary table comparing the potential for human exposure associated with each use follow.

F. Conditions of Use on Timber

When forests are "managed" with the aim of commercial timber production, herbicide use is common. The purpose is to control the growth of broadleaf plants, or hardwood, which compete with the conifers for light and moisture. The need for herbicides increases as a function of precipitation since rainfall encourages the growth of these competing species. In a managed forest, the acreage is subdivided into cutting units, each of which is treated with herbicides perhaps 2-3 times in the life cycle of the species: once for site preparation (The cutting unit is cleared and the site sprayed to rid it of all growth prior to planting); again 35 years later for "conifer release" (the site is sprayed to cut back the faster-growing young alder); and perhaps again the following year if "release" was not totally successful. The cutting unit -- which may range in size from 10-1,000 acres -- is not treated again until the stand has attained maturity and been harvested and the land is ready for replanting. Both federal and corporate owners report that they aim to treat 2-4% of their total acreage in any one year. The time of treatment depends upon weather conditions at the cutting unit but it typically takes place in the late spring. The average application rate is 2-4 lbs of active ingredient per acre, and the herbicide is sprayed on by helicopter.

G. Conditions of Use on Rice

In rice cultivation, 2,4,5-T is used to control weeds, particularly indigo, whose presence in the harvested crop reduces its commercial value by affecting the appearance of the product. 2,4,5-T is typically applied annually, at an average rate of 1-1.5 lbs per acre. (2,4,5-T amine is used rather than the 2,4,5-T ester used in brush control.)

Planting takes place in late April and the rice is grown under irrigation. Herbicide is applied before the rice head is formed. The herbicide is sprayed from a fixed-wing aircraft, usually 3-10 feet from the ground. At the proper time in internodal growth, the paddies are drained, 2,4,5-T laid down, and then the areas are flooded once again until harvesting in September and October.

There are short-grain, medium-grain and long-grain varieties of rice; each nodes at a different rate. Thus, treatment time is a function of rice variety. Owners typically plant a mixture of rice varieties and hence, may treat their acreage at different times during the season. The average size of a treatment area is 120-150 acres. Most applications occur in late June or early July, but the range extends from mid-May through mid-August.

For the sake of the soil, rice is alternated with another crop, usually soybean, once or twice in a three-year period. Soybeans are broadleaf plants and hence 2,4,5-T is not used on this crop. Because these sensitive crops are frequently contiguous to rice fields, appli-

cators do attempt to minimize drift.

It is important to note that other pesticides are used in combination with 2,4,5-T in caring for rice crops; thus, populations living near rice fields may be exposed to several chemicals.

H. Comparison of Rice and Timber Uses in Respect to Factors Affecting Potential for Human Exposure

1. Mode of Application

In the forest, the applications are made by helicopter at a considerable distance from the ground; in the rice paddies the applications are made by low-flying fixed-wing aircraft. One might expect that there would be more drift in connection with the timber applications, but that smaller amounts of herbicide would be reaching the ground.

2. Topography

The mountainous terrain of forests, which makes control of the spray nozzles difficult, may provide a greater potential for exposure as a result of drift than the flat rice paddies.

3. Population Density

Population is likely to be smaller and less evenly distributed in mountainous areas than in flat agricultural areas (Census and topographical map data show this to be true.)

4. Sunlight

Dioxin breaks down readily only in the presence of sunlight; there is less exposure to sunlight under a forest canopy than in an agricultural setting.

5. Intensity of Exposure

The application rate on rice is half that of timber 1 lb per acre on average compared with 2 lbs per acre.

6. Frequency of Treatment

Rice paddies are treated annually while individual cutting units within a forest are treated only 2-3 times over several decades.

7. Proportion of the Population Potentially Exposed

Given that rice is typically alternated with another crop, we estimate that from 50-60% of the population residing in rice farming areas is likely to be exposed in any year. In the forests only 2-4% of the total acreage is treated in any year, and thus, only a small portion of the population is likely to be exposed each year.

8. Availability of Records

Regulation of 2,4,5-T and other phenoxy herbicides has largely been directed at the protection of susceptible non-target crops. For this reason, agricultural uses have traditionally been much more closely regulated than forest uses, and public records of such applications are fairly complete. There has been far less public regulation of herbicide applications in timbered areas, where damage from drift onto sensitive crops is less likely. Maintenance of application records has been left largely up to the individual owners or commercial applicators, and hence the quality and availability of documented herbicide use in this sector varies.

I. SUMMARY

The uses of 2,4,5-T in rice and timber cultivation represent distinctly different types of exposure to this chemical. The use of the herbicide on rice may produce a chronic, low-level exposure. Since farm populations tend to be stable, many individuals living in rice-growing areas may have had lifetime exposure to accumulating concentrations of 2,4,5-T as well as other pesticides with unknown reproduction risks to human. Of special interest is the fact that there is a continuing use of 2,4,5-T presenting the possibility of either a cross-sectional or prospective study. Although the level of exposure in agricultural areas is probably lower than in timbered areas, the population at risk is larger.

In contrast, herbicide use on forests may produce sporadic and more intense exposures, which occur perhaps 2-4 times in the life of any individual. Although conditions in forests may lead to larger doses of exposure than in the rice area, the population at risk is smaller. In contrast to the residents around rice fields, herbicide use on timber has been suspended and its effects can only be studied retrospectively.

IV. Selection of Sites for Review

Queries to individuals knowledgeable about herbicide use on timber and rice identified the following areas of heavy use:

- 1) Timber: The Pacific Northwest, specifically the coastal corridor and especially Oregon; The Great Lakes; the South Central and Gulf Coast regions.
- 2) Rice: Mississippi, Louisiana, Texas, Arkansas, and California.

In the timberlands, even though application practices are similar from place to place, climate and topography vary so that 2,4,5-T use is heaviest in the Pacific Northwest, with the South ranking next and the Great Lakes region following.

Of the heavy rice-growing states, Arkansas proved to be the heaviest user of 2,4,5-T. Only MCPA is used in California and Texas because of the problem of drift onto non-target vegetation. 2,4,5-T is used in Louisiana and Mississippi, but less acreage is planted in rice in these states than in Arkansas. In Arkansas 2,4,5-T has also been used in a large expanse of timberlands for more than 20 years.

Thus the Pacific Northwest, both Oregon and Washington and Arkansas were selected for site visits.

V. Data-Gathering Procedures

A. Basic Approach

In Table 1, we outline the types of data we attempted to obtain for each site visited.

TABLE 1
2,4,5-T FEASIBILITY STUDY:
Data Gathering Objectives

EXPOSURE	EXPOSED POPULATION	REPRODUCTIVE OUTCOME	UNEXPOSED
Areas of high use of 2,4,5-T: proportion of use for forest, crops, roadside, range, right-of-ways.	Size and distribution of population in exposed area.	Estimate of medically unattended reproductive events.	Deferred, except for decision about whether to draw the unexposed sample from the same geographic areas as the exposed sample.
Patterns of ownership by areas and type of use.	Size and fertility of population of reproductive age.	Where and when in pregnancy medical attention is sought; what information is recorded regarding the event.	
Samples of existing data on 2,4,5-T applications, by type of owner: dates; locations; amounts; composition.	Estimates of the number of pregnancies at risk of exposure per year.	What information is recorded regarding the patient (i.e., data on potentially confounding variables). SEE APPENDED INTERVIEW FORMS FOR FURTHER DETAIL.	
Accessibility of exposure records.	Information relating to demographic and control variables: race mother's education urban/rural residence % illegitimate births % births to women 19 % births to women 35	Accessibility of records.	
Concomitant exposures: -- fungicides -- insecticides -- other chemicals	Medical care patterns.		
Fate in the environment: possibility of continuing exposure.			

The organization of the table reflects the basic approach. In each area we attempted first to find where there had been heavy use of 2,4,5-T, or 2,4,5-T and 2,4,-D in combination; to identify the major users; and to evaluate the type and accessibility of records of herbicide applications.

Having determined where herbicide use had been heaviest, we then gathered information about the population potentially exposed. Our principal objective here was to establish whether the residents in or near areas of herbicide applications provided sufficient numbers of reproductive events to permit examination of the research question. We also had to estimate the proportion of reproductive events for which there might be no official records. In addition to these quantitative data, we also attempted to construct a social and health profile of the local population, particularly those of reproductive age. Finally, we investigated medical service use, medical practices, and the nature and availability of medical records on reproductive outcomes. The questionnaires we developed for physicians and hospitals, inquiring about their obstetric and recordkeeping practices, are appended. These data will be discussed below in connection with the site visits.

VI. Site Visit 1: Pacific Northwest

In the Pacific Northwest our aim was to reevaluate the original Alsea area as a site for further study and to assess the research potential of other locations in Oregon and Washington.

A. Exposure Data

1. Patterns of 2,4,5-T Use in Northwest Timberlands: Use of 2,4,5-T in the Northwest occurs almost entirely west of the Cascade Mountain Ridge, in the Coastal Range. This is chiefly a reflection of precipitation patterns. As rainfall increases, so does the growth of the broadleaf trees like the alder, which compete with conifers for sunlight and moisture. Average annual rainfall is 12 inches east of the Cascades, 35 inches just west of the ridge, and 80 inches along the coast. The U.S. Forest Service estimates that 80% or more of all phenoxy use in Oregon and Washington occurs from Gray's Harbor County in Washington south along the coast. North of Gray's Harbor there is more hemlock than Douglas fir, and hemlock has an easier time penetrating broadleaf trees.
2. Species Produced: Douglas fir.
3. Application Rate: An average of 2 lbs of active ingredient per acre.

4. Size of Treatment Unit: The average cutting unit in the Oregon national forests is about 40 acres. This may mean that depending upon where one lives, one may be exposed to treatment at multiple sites.
5. Topography: The steep hills and narrow valleys characteristic of the Coastal Range are thought to promote herbicide exposure through a funneling effect. There is also a network of streams running through the mountains which despite buffer strips becomes contaminated with herbicide.
6. Population Density: Since the rugged terrain restricts accessibility, population tends to cluster in the narrow valley bottoms. However, particularly in the Siuslaw, the slopes are punctuated with valleys and there is more distribution of population through the forest than might occur if the drainage were very long and there were fewer valleys.
7. Land Ownership: Ownership of the timberlands along the coast and east to the Cascades is of three types: (1) Federal (owned either by the U.S. Department of Agriculture Forest Service or the Department of Interior Bureau of Land Management); (2) State; and (3) corporate.

Following is a Forest Service map of the area, showing county boundaries and locations of national forests. In counties like Coos, Clatsop and Tillamook, and parts of Lincoln, the forests are owned by corporations or the state. Gray's Harbor, Pacific, and Lewis counties in Washington, considered to contain extremely productive timberlands, are largely the domain of corporate holders. In the strip just to the east, between the coast and the Cascades, much of the timbered areas belongs to the Bureau of Land Management and to smaller private holders.

Both Federal agencies consider themselves minor users of phenoxies compared to the state and corporate owners because of the Federal government's more cautious policy regarding the use of chemicals.

8. Availability of Records, by Type of Owner

- a. Federal: Federal agencies expressed an interest and a willingness to cooperate. Samples of the forms used to document herbicide applications were obtained. These records are said to be kept on file for a minimum of five years.
- b. Oregon State: While state officials view themselves as closely allied to the private sector, they are willing to cooperate in "responsible" research. Records are said to be accessible and are maintained for a minimum of three years. Sample forms were obtained.
- c. Washington State: This agency reported that, with the exception of the last few years, neither locations, amounts nor formulations of herbicide applications are accurately reported in their records.
- d. Corporate Owners: The Washington State Forest Association represents

all of the commercial users. In order to gain access to the data on herbicide applications of the corporations represented by the Association it will be necessary to obtain approval of the proposed research from the Association.

9. Summary

A. Pacific Northwest as a Site for Study

In regard to exposure, the following points must be addressed in considering the Pacific Northwest as a site for study:

- a. the low frequency of exposure;
 - b. seasonality of applications; and
 - c. documentation of herbicide use.
- a. Exposure Frequency: The potential for human exposure associated with forest use of 2,4,5-T may be high, but because the portion of forested land treated in any year is small, it will be difficult to develop the sample size of exposed pregnancies sufficient to give a study reasonable statistical power.
- b. Seasonality: The use of 2,4,5-T on forests occurs in the spring, and sometimes in the summer. Therefore, exposure as defined by application practices is seasonal. It is not clear whether the frequency of spontaneous abortion varies with season, since this question has been examined only on occasion and never in rural areas of the United States. McDonald (1971) in Canada found a slight, but nonsignificant, increase in the loss of pregnancies conceived in March-June which she related to winter-spring infections. Nelson et al. (1971), of the Center for Disease Control, reported no seasonal pattern in a three-year series of aborted fetuses. A study of seasonality in relation to reported fetal loss in New York City, which included spontaneous abortions less than 20 weeks gestation, observed a trough for August-November conceptions and a peak among January-April conceptions (N.Y.C. Dept. of Health, 1971). These variations were slight and were confined to early losses and to the Puerto Rican and non-white. In our hospital-based study in New York City, we have not detected a seasonal trend in the frequency of spontaneous abortion. Since these results were all obtained in urban areas, it is possible that a seasonal trend in abortion exists in rural areas. Thus it is prudent to control for season (month) of conception in any design to investigate the relation of herbicide exposure to abortion.
- c. Documentation: The availability and accessibility of data on herbicide applications present a potential problem, especially in the state of Washington.

B. Population at Risk of Exposure

Vital statistics, population data and discussions with state and county health officials formed the basis for understanding the general health and habits of the population which might be exposed to spraying, as well as their fertility rate and patterns of medical service use. The demographic and spray data were used to estimate the number of pregnancies per year at risk of exposure.

To supplement visual impressions, U.S. Geological Survey dwelling maps were obtained to determine the distribution of population throughout the forested areas.

Anecdotal evidence was gathered regarding the attitudes of local residents toward herbicide use and toward research on its relationship to health effects.

The following issues bear on the suitability of the Pacific Northwest coastal region for research on the reproductive effects of herbicide use:

1. the lifestyle of residents;
2. possible reporting bias; and
3. potential sample size.

1. Lifestyle: One criticism of EPA's Alsea study was that the lifestyle of the population living in the forested areas of the Pacific Northwest particularly that of recent and younger residents, might have operated to confound the analysis. It was claimed that this alternative lifestyle involved drugs, diet and habits of hygiene that themselves were risk factors for spontaneous abortion. In another vein, local informants have noted that among this group there is a trend to alternative health care that might make it difficult to document pregnancy outcome.

On the first point, it was not possible to develop hard information. Impressionistic evidence, however, suggests that under the rubric "alternative" fall a variety of lifestyles which may, or may not, incorporate drug use or extreme diets which, in turn, may or may not increase the risk of spontaneous abortion. To our knowledge, organic or macrobiotic diets have not been examined in relation to pregnancy outcome. In our study in New York City, heroin use, but not occasional marijuana use, was associated with spontaneous abortion.

If one considers the frequency of illegitimate births or month of first prenatal visit as indirect measures of lifestyle, then statistics for counties along the coastal corridor suggest there is considerable variation. In one county for instance, 67% of women have made a pre-

natal visit by the second trimester of pregnancy and only 6% of births are illegitimate. The comparable figures for another county located are 37% and 17%.

Whether and how an alternative lifestyle affects the risk of spontaneous abortions may be a matter for speculation; however, it is unlikely that lifestyle varies with exposure. If a sample is drawn solely from the forest area, it is reasonable to expect that the unknown effects of "lifestyle" will be similar among exposed and unexposed residents.

2. Reporting Bias: In Oregon particularly, but also in Washington and Northern California, herbicide use in forest management is a major local issue pitting those with economic ties to the timber industry against environmentalists. The clash of attitudes gets considerable coverage in the local media, and groups have formed to promote the opposing positions' e.g., Women for Timber and Citizens Against Active Sprays.

Although we were not able to examine the question of bias systematically, clearly attitudes have been formed regarding the health effects of herbicides, giving grounds for concern about the potential for biased reporting. If overreporting were the only possibility, one could confront the problem by requiring validation of all pregnancies reported. Local health officials currently believe, however, that health problems may be underreported because local residents fear the loss of their economic base. The risk of this bias, which is far more difficult to assess since one cannot check records on pregnancies that are not reported, argues against collecting reproductive information by interview.

3. Potential Sample Size: In designing a study, we would require a sample of sufficient size to have at least an 80% chance of detecting an increase in risk of predetermined size. All other things being equal, as sample size decreases, so does the statistical power to detect an effect, if it is indeed present. The sample size for a study of 2,4,5-T exposure and reproductive outcome in the Pacific Northwest is likely to be small for several reasons:

a. The forested areas are sparsely settled, and there is little point to including more populous urban centers in the sample since they are not at risk of exposure and hence cannot be informative as to the presence or absence of effects.

b. Only a proportion of the population is susceptible to the effect under study; that is, only the population of reproductive age.

c. Since only a small percentage of total forest area is treated with herbicides in any one year, only a correspondingly small proportion of the population can be exposed in any year. Estimates of sample size have been developed below as part of the preliminary study design.

C. Reproductive Outcome Data

Physician records in two sample counties (counties A and B) in Oregon were reviewed in order to assess their utility either as a source for ascertaining pregnancies or validating reports of pregnancy obtained through interview. The attempt was made to interview virtually all physicians who were, or had been, treating obstetric patients in the sample counties, rather than visiting a portion of the physicians in a larger number of counties. This approach seemed particularly useful since the strong possibility of reporting bias in the population suggested that a review of medical records, rather than personal interviews, was likely to comprise the data source.

1. Data-Collection: Appendix 1 contains the interview schedules which were administered to physicians and to hospital personnel. In each office we asked to review a random sample of charts to note the scope and legibility of information included and to determine whether short-cuts existed to locating pregnancies within the chart. The central questions we sought to answer were:

- a. What proportion of local obstetric care does the office deliver?
This information helped to weight the data from each office when we attempted to describe the characteristics of the entire county.
- b. What number of deliveries and of spontaneous abortions are treated by this facility each year?
This information was useful in estimating the potential sample size.
- c. How soon after their last menstrual period are women usually seen for diagnosis of pregnancy?
This information helped us gauge how many early spontaneous abortions might be missed in a medical record review.
- d. How often, if ever, are spontaneous abortions documented in the medical records?
In particular, we sought to determine whether a telephone report of a miscarriage, in the absence of an office visit, would be recorded.
- e. What information is routinely obtained regarding the characteristics of the couple who have experienced a spontaneous abortion?
Information on this question provides knowledge of whether records could supply the necessary data on potentially confounding variables.
- f. What proportion of women experiencing spontaneous abortions are hospitalized?

- g. Lastly, would the physician agree to a record search were a new study to be undertaken?

Following are background information and a summary of findings from the medical records survey.

County A

Long, narrow coastal county.
Population = 31,000

Economy: depends on tourism,
timber, fishing.

Medical facilities: Three small
hospitals of 40-50 beds each.
Obstetric patients are treated
by general practitioners; almost
all obstetric admissions to one
hospital are welfare patients.

In 1978, there were 471 births
(15.1/1000); 270 (60%) of these
took place within the county. Of
the 60%, 9% occurred out-of-hospital.
In other words, some 50% of births
were not attended by doctors from
County A. It is believed that most
of the obstetric cases going out of
county A deliver in an adjacent county.
Those delivering in-county tend to be
less affluent; the illegitimacy rate
among these women is 27%.

County B

Smaller but more populous than
county A. Population = 68,000

Economy: Somewhat higher
socioeconomic status than county
A; economy is university and
industry related.

Medical facilities: One large
hospital of 160 beds. About 15
physicians have seen obstetric
patients at some time over the last
10 years. Included here are nine
obstetricians and six general
practitioners.

In 1978, there were 804 births
(11.7/1000) to county residents,
yet almost 1200 births occurred
within the county, presumably
because the obstetricians provide
care to women from other counties.
About 3% of births occur out-of-
hospital; illegitimacy rate is 6%.

2. Conclusion: From our tally of the questionnaire data, we draw the following tentative conclusions:

- a. The great majority of physician records would be open to us if we were to undertake a study.
- b. At least 90%, probably close to 100%, of livebirths could be ascertained or validated from these records since even those delivering out-of-hospital usually have at least one prenatal visit.
- c. The major loss of information on reproductive events, should information be confined to these records, would be:
 1. Very early, recognized but unreported spontaneous abortions, believed by physicians to be a very small proportion of all spontaneous abortions.
 2. Early spontaneous abortions, reported but not preceded by a prenatal visit: It appears from the data that as many as 50% of spontaneous abortions prior to 12 weeks gestation are either not recorded in the medical record or are recorded, but with little data.
- d. It appears that data on potentially confounding variables (i.e., maternal characteristics) will be reasonably complete in these records from about 1970 on for term pregnancies, but incomplete for pregnancies ending in spontaneous abortion.
- e. A survey of all pregnancies would be possible from these charts, with the limitations mentioned above, but would require a review of the entire chart for every woman in order to identify all spontaneous abortions. Although many of the records have a separate obstetric page, it may not contain information on spontaneous abortions, but only data on pregnancies going to term.
- f. Physician records should extend data on spontaneous abortion considerably beyond that obtained through hospital records.

D. Development of a Study Design in the Northwest Forests

The development of a research design to examine the relation of an environmental factor like 2,4,5-T to reproductive outcome is contingent both on the hypotheses to be tested and the special characteristics of the population to be studied. We consider below: (1) the previous literature regarding the relation of 2,4,5-T to reproductive outcome and the hypotheses generated by this work; and (2) special characteristics relating to exposure and data collection in the Pacific Northwest. Based on these considerations, we then set out the conclusions we have

reached regarding study design for this location, and discuss the strengths and limitations of this approach.

1. Review of Literature and Hypotheses

a. Route of Exposure to the Parent: Exposure via ingestion is the only route which has been examined in laboratory studies of 2,4,5-T and/or TCDD. Exposure via inhalation and skin absorption -- the routes of exposure one would associate with herbicide applications -- has not been studied in animals, so it is not known whether response varies with the route of exposure.

Whether and to what extent 2,4,5-T remains in the environment following spray applications is difficult to gauge. There may be continued exposure via ingestion of contaminated food or water; however, this is difficult to determine since residue data are sporadic, conflicting and subject to reporting bias. In the absence of data on the presence of 2,4,5-T in the water and food, it will be necessary to define exposure as residential proximity to aerial application sites and to infer the route and timing of exposure from spray data.

b. Route and Timing of Exposure to the Conceptus: We reviewed laboratory and epidemiologic evidence relating either TCDD or 2,4,5-T to reproduction in order to determine whether the route to the conceptus is likely to be through the female parent, the male parent, or both.

A paternal influence has been suggested by the allegations of Vietnam veterans exposed to Agent Orange, and by unpublished data which compared the occurrence of birth defects among offspring born to exposed Vietnamese fathers and unexposed mothers with that among offspring of couples where both parents were unexposed to herbicides (Tung et al, 1979). Although the data are very suggestive, a systematic investigation has not been carried out, and firm conclusions can not be drawn. As yet, there is no published report in which exposure of male animals to 2,4,5-T has been examined in relation to reproductive outcome. A three-generation rat study does not permit evaluation of a paternal effect separate from maternal effects (Murray et al, 1978).

However, the question of male influence has been examined in relation to TCDD. Unlike the study of 2,4,5-T, a three-generation study of TCDD included a cross-mating experiment, where the effects of both maternal and paternal exposure were assessed in rats (Smith et al, 1979). Following exposure of female rats, nonsignificant trend to fewer implantations and a significant increase in resorptions were observed; exposure of the male was not associated with infertility or pre- or post implantation loss. Negative results have also been reported for exposure of the male on the dominant lethal test in the mouse and in the rat; however, this test is insensitive to all but strong mutagens.

At this time, it is not possible to rule out the possibility of an effect operating through the father as well as through the mother. This suggests that exposure prior to conception must be considered as well as exposure during pregnancy. When a paternal influence is hypothesized, the relevant period for exposure in studies of reproductive effects is sometimes defined as the approximately three months it takes for sperm to fully regenerate.

In regard to the female, the animal studies establish the presence of effects in association with exposure during pregnancy but do not allow one to determine whether preconception maternal exposure of the female, separate from exposure during gestation, has adverse reproductive effects.

There is no information upon which to judge at what time during pregnancy this agent might operate. However, since spontaneous abortion, the major outcome of interest, is by definition fetal death occurring before 28 weeks gestation, we have considered exposures only up to week 24 of gestation following the last menstrual period.

c. Summary: In the absence of strong evidence that a reproductive effect of 2,4,5-T is confined to one or the other parent, or a particular time period, we propose to examine whether exposure to 2,4,5-T (defined by proximity to aerial applications) occurring to either parent from six months prior to conception until 24 weeks after the last menstrual period (LMP) is associated with spontaneous abortion. As we discuss below, our definition of exposure prohibits our distinguishing between maternal and paternal preconception exposure in the proposed study. We aim, however, to evaluate the effects of preconception and post conception exposure separately.

2. Conditions Affecting Study Design Decisions: Based on the nature of the 2,4,5-T use under consideration and of the candidate study area, certain factors emerge which influence the design of the study. These factors have been described in the preceding text.

Following is a table which sets out the factors or problems to be dealt with, and the corresponding decision about study design which was made to cope with each condition. This table is followed by:

- a. a statement of the hypothesis to be tested in such a study;
- b. a discussion of the study design options;
- c. estimates of the sample size potentially available for study and a description of the analysis;
- d. a discussion of the statistical power of the analysis; and
- e. Conclusion.

Table 2

Conditions Affecting Design Decisions for 2,4,5-T Study in
Pacific Northwest Forests

<u>Condition</u>	<u>Design Decision</u>
1. Suspended use of herbicide	→ Retrospective study → Indirect measure of exposure
2. Possibility of reporting bias	→ Record review rather than interview as source of data
3. Different period at risk of exposure for spontaneous abortions and livebirths	→ Control length of gestation to equalize period at risk ----- Case-control rather than cohort design
4. Possible confounding effects of lifestyle	→ Restrict analysis to forest population
5. Low prevalence of exposure	
6. Lack of data on potentially confounding variables	
7. Seasonality of exposure (and possibly of outcome)	→ Control for time of conception
8. Small sample residing in forest	→ Extend study area down coastal corridor
	→ Maximize time period of study
	→ Increase size of comparison population

a. Hypothesis to be Tested: The hypothesis which could be tested in the Pacific Northwest timberlands is whether acute exposure to 2,4,5-T, either prior to conception or during pregnancy, is associated with spontaneous abortion. Although it is theoretically possible for the same agent to have an effect at both periods, it is more likely that an effect will be specific to one or the other time in relation to conception and hence it is desirable to examine the questions separately.

In addition to spontaneous abortion, other outcomes of pregnancy such as birthweight and birth defects could be studied in relation to 2,4,5-T exposure.

b. Discussion of Study Design Options

1. Retrospective Data Collection: The use of 2,4,5-T in forest management has been suspended since after the 1978 spraying season. Therefore, any study of reproductive effects in timberlands must be retrospective, attempting to relate history of reproductive events to history of exposure. Even if reliable and noninvasive biochemical measures of 2,4,5-T existed, the retrospective design obliges use of an indirect measure of exposure. The available definition of exposure -- residential proximity to aerial application sites -- serves as an indicator that the potential for exposure existed: clearly absorbed dose could vary widely in a population so defined as "exposed." The possibility of misclassifying exposed and unexposed individuals when using this operational measure of exposure should be borne in mind.

2. Source of Data on Pregnancies: The major determinant of study design has been the threat of reporting bias in forest communities. Given its importance, it is regrettable that we have no firm evidence that the threat is real. The fact that the relation of herbicide use to reproductive health has already been studied in the Northwest, however, argues strongly for use of a convincingly bias-free source of data in subsequent research. Thus, we have selected physician records rather than interviews as the method of data collection.

The decision to use physician records to collect data pertaining to all reported reproductive events has strengths as well as limitations. With this data source, neither biased responses nor a high nonresponse rate can affect study results. Using medical records as the data source means, however, that some recognized spontaneous abortions may be missed; that data on potentially confounding variables may not be present consistently enough to permit analysis; and that confirmation of residence and additional exposure information which might be obtained by interview must be forsaken. Since the residential information contained in the chart may not accurately reflect residence during spraying, when couples may have been away from home, the proposed analysis using place of residence to evaluate exposure status is ecologic. The potential for error is greater for full-term pregnancies, where more absences from the

home may occur in the nine gestation months, than for spontaneous abortions, which are of shorter gestation.

3. Case-Control Design: The difference in length of gestation for spontaneous abortions and for term pregnancies has other more serious implications for study design. Ordinarily, as in this instance, when exposure to the factor under study is less common than the outcome of interest (the prevalence of exposure in the population is estimated to be about 2-4%, while the usual rate of spontaneous abortion is about 15% of recognized pregnancies), a cohort analysis provides the most powerful test of the study hypothesis. Special problems arise, however, in applying this approach to the study of spontaneous abortion in relation to an exposure occurring during pregnancy. Since the period at risk of exposure increases with increasing length of pregnancy, there is a built-in bias to define term pregnancies as "exposed", and thus, associate exposure with the satisfactory outcome.

A case-control analysis of the data, where cases are pregnancies ending in spontaneous abortion (fetal death at 28 weeks gestation or earlier) and controls are pregnancies ending after 28 weeks gestation, can meet the problem outlined above by considering exposure in the control pregnancy only up to the date of abortion of the referent case. It would be impossible in the small Oregon sample to equalize the period at risk for births and abortions in a cohort analysis. A lifetable analysis in days (or weeks) of gestation would be needed to ensure that successful pregnancies were not at greater risk of exposure than pregnancies ending in abortion, because of their increased gestation. The number of pregnancies in the Pacific Northwest forest area are too few to contemplate this approach. Failure to control gestation in relation to risk of exposure will not merely dilute an effect, if one exists, but will actually bias a study against detecting an effect. Thus, the gain in statistical power that would ordinarily result from organizing the data into cohorts of exposed and unexposed pregnancies is offset by the inherent bias that exists in studying spontaneous abortion in relation to an exposure which occurs during pregnancy. This argues for a case-control analysis. Since age is associated with abortion and often with habits, such as smoking, which also are associated with abortion, we propose also that cases and controls be matched loosely for maternal age (30 years, 30+ years).

4-6. The Forest Residents: The decision to restrict analysis to comparisons of women living in forest areas provides an indirect control for the unknown effects of lifestyle on reproduction. If the alleged higher risk of spontaneous abortion in timbered areas as compared with other areas is truly a reflection of the population's lifestyle and not of their exposure to herbicides, then comparisons made within forest areas, where lifestyle and service use patterns should be similar, will reveal this. If, on the other hand, herbicide exposure does have an effect, that too should be detectable given that herbicide applications within the forests are highly variable with respect to place and year.

The focus on forested areas also maximizes the prevalence of exposure by excluding noninformative pregnancies -- that is, those that are never at risk of exposure. It also compensates somewhat for the lack of systematically collected data on potentially confounding variables such as smoking, alcohol drinking and drug use because of the similarity in lifestyle of the residents.

7. Seasonality: In order to control for the potential confounding of the effects of season of conception with timing of spraying, cases and controls should be matched for month of LMP so that the frequency of exposure can be compared among pregnancies conceived at similar periods.

c. Estimates of Sample Size and Description of the Analysis

The limiting factor on sample size is the number of spontaneous abortions occurring in the Oregon coastal forests over a five-year period. To boost sample size, we have extended the study period to five years, the longest period for which exposure data are reported to be reliably available, and have considered the study area to be the entire coastal corridor of Oregon forests.

The estimated number of cases was generated as follows:

1. The number of livebirths occurring in 1978 was calculated for the population falling within the Oregon coastal forests: $n=1400$ livebirths.
2. The number of spontaneous abortions occurring each year was estimated assuming that livebirths represent 85% of recognized pregnancies: $n=241$ spontaneous abortions.
3. Based on results of our medical records survey, it was assumed that as few as 50% of the abortions occurring would be found (with usable data) in physician records. (This assumption may be somewhat strigent.) $n=120$ spontaneous abortion found.
4. The number of ascertained abortions per year was multiplied by five to get the total for the study period.

We estimate that 600 abortions will be ascertained through a review of all physician records in the forest region.

Since spraying occurs only in the spring-summer, pregnancies occurring at different times of the year vary in the risk of exposure either prior to conception or during gestation. We propose that the exposure status of each conception, whether a case or control, could be described in one of five categories: exposed 4-6 months prior to LMP; exposed 1-3 months prior to LMP; exposed in the 1-3 months following LMP; exposed in the 4-6 months following LMP; not exposed 1-6 months prior to LMP or 1-6 months following LMP, that is, not exposed in any of these four time

periods. For pregnancies ending within 28 weeks of the LMP, these categories of exposure status are mutually exclusive, provided spraying does not occur twice in the same location in any one year. As mentioned earlier, the gestation of controls considered in assigning exposure status ends at the time of abortion for the referent case. A contingency table analysis would be used to compare the distributions of cases and controls with respect to these five categories of exposure.

Given that approximately 4% of the forest is sprayed each year, we estimate that 1% of the sample will fall into each of the four exposure categories and the remaining 96% will be unexposed both in the six months prior to conception and in the first six months of gestation in any year.

d. Statistical Power

In the next table we have illustrated the size of the effect which could be detected with 80% power ($\alpha = .05$, two-tailed) if the effect of exposure is confined to one three-month period prior to or during gestation and 600 cases are compared with 600 controls. (In the example, we show the effect as occurring only with exposure during the first trimester of pregnancy.) We have also carried out the same calculation also assuming two controls were selected for each case. The effect is shown as the increase in exposure frequency among cases relative to their controls.

As may be seen from the second column of the table, only large effects (odds ratio = 4.1, or 2.7 in the case of two controls per case) could be excluded with confidence if the distributions did not differ significantly. On the other hand, if exposure had an effect during more than one three-month period (e.g., throughout the first two trimesters of pregnancy) an odds ratios of 2.7 could be detected with equal numbers of cases and controls.

Perhaps it should be mentioned that three factors known to be associated with spontaneous abortion each have odds ratios less than those set out in the table. The odds associated with heavy smoking are 1.7; with drinking daily, 2.5; and with prior spontaneous abortions, 2.0. Thus, the effects likely to be detected in the study described here, are larger in size than those of previously identified risk factors. Also, it should be mentioned that the sample described here may include multiple pregnancies to the same couple, raising the problem of nonindependence in the unit of analysis. If the sample were restricted to one pregnancy per couple, the sample size, and consequently the power of the test, would be further reduced.

Table 3

ILLUSTRATION OF THE EFFECT SIZES WHICH COULD BE DETECTED IN THE
OREGON FOREST SAMPLE (WITH 80% POWER*) USING ONE CONTROL PER CASE
AND USING TWO CONTROLS PER CASE

	<u>Expected % Distribution of Sample</u>	<u>% Distribution Which Could Be Detected as Significantly Different From Expected If N cases =600 & N controls =600</u>	<u>% Distribution Which Could Be Detected as Significantly Different From Expected If N cases =600 & N controls =1200</u>
Exposed 4-6 months prior to LMP	1.0	1.0	1.0
Exposed 1-3 months prior to LMP	1.0	1.0	1.0
Exposed 1-3 months after LMP	1.0	4.0 (odds=4.1)	2.7 (odds=2.7)
Exposed 4-6 months after LMP	1.0	1.0	1.0
Not exposed	96.0	93.0	94.0

* =.05, two-tailed

e. Conclusion

The statistical power of the analysis might be greater than the above estimate if:

1. The prevalence of exposure is substantially higher than has been estimated, perhaps because the topography of the West Coast forests produces exposures in a larger proportion of population than is suggested by the percentage of treated land. For example, if the prevalence of exposure was as high as 8% rather than the 4% estimated, the detectable odds ratio for an effect confined to one three-month period would be 2.8.
2. Ascertainment of abortions in physicians' records is better than the 50% estimated; if ascertainment improved from 50% to 70%, the number of cases would increase from 600 to 840. As an indication of how this would improve power, the detectable odds ratio for an effect confined to one three-month period is changed from 4.1 to 3.3.
3. Assuming the preceding estimates of exposure frequency and sample size set out in (d) above are correct, an increase in sample size would produce an improvement in the power to detect a more modest effect. This could be accomplished by extending the study to include residents in the Northern California forests. This last suggestion may be the most pragmatic. Certainly based on the present estimates of the sample available, the power of the study set out here is not adequate to search for moderate effects of exposure to 2,4,5-T (odds ratios of 1.8 or 2.0).

In sum, we consider that the Oregon coastal forests cannot provide a sample sufficient to test whether exposure to 2,4,5-T has a moderate association with spontaneous abortion.

In addition to the problem of sample size one must worry about the further reduction in power stemming from the imprecision of the operational measure of exposure.

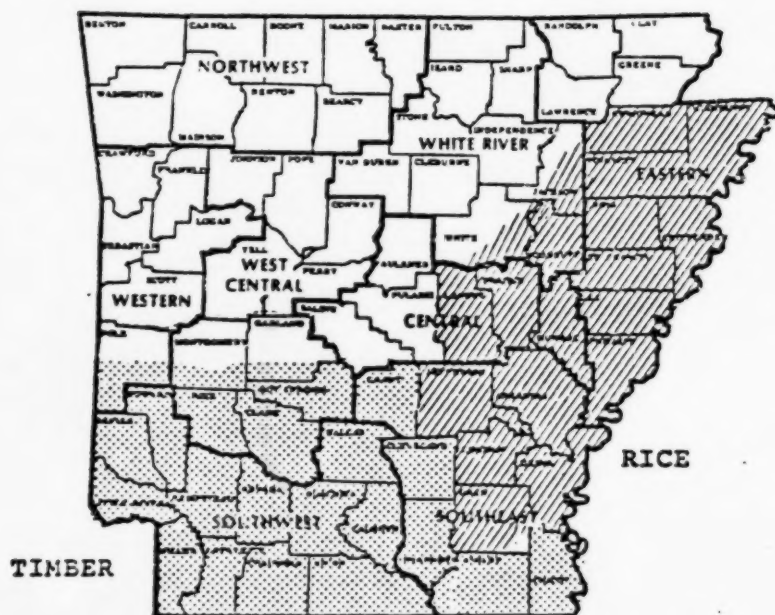
Further, the use of medical records as the data source means that the analysis is essentially ecologic and also requires the assumption that use of medical care does not relate to risk of exposure.

References Cited

- McDonald, A.D. 1971. Seasonal distribution of abortions. Br J Pev Soc Med, 25: 222-224.
- Murray, F.J., Smith, F.A., Nitschke, K.D., Humiston, C.G., Kociba, R.J., and B.A. Schwetz. 1979. Three-generation reproduction study of rats given 2,3,7,8- Tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol. Appl. Pharmacol. In press.
- Nelson, T., Oakley, G.P. and T.H. Shepard. 1971. Collection of human embryos and fetuses. In Monitoring, Birth Defects, and Environment: The Problem of Surveillance, Hook, E.B., Janerich, D.T. and I.H. Porter, eds., pp. 45-64.
- New York City Department of Health. 1971. The Influence of Season of Conception on Obstetric Casualties. New York: Health Services Administration.
- Smith, F.A., Schwetz, B.A., Murray, F.J., Crawford, A.A., John, J.A., Kociba, R.J. and C.G. Humiston. 1978. Three generation reproduction study of rats ingesting 2,4,5-Trichlorophenoxyacetic acid in the diet. Unpublished manuscript.
- Tung, Ton that, Lang, Ton duc, and Do duc Van. 1979. The question of mutagenic effects on the second generation after exposure to herbicides. Unpublished manuscript.
- U.S. Environmental Protection Agency, Environmental Studies Program. 1979. Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Practices.

VII. Site Visit 2: Arkansas

Arkansas was of special interest as a potential study site because it presented an opportunity to examine the use of 2,4,5-T on both timber and rice in contiguous areas and thus, in relation to a homogeneous population. The map which follows shows the areas within the state where rice and timber are cultivated commercially. Prior to the site visit, two rice counties (counties C and D) and two timber counties (counties E and F) were selected for investigation. State and local officials considered these counties to be typical of the rice and timber cultivating areas. Our findings are summarized below.



ARKANSAS

A. Exposure Data

1. Timber

The similarities and differences which were noted between the treated forests in Arkansas and in the Pacific Northwest are described below.

a. Species produced: In Arkansas, pine is produced, rather than the Douglas fir of the Northwest. Pine matures more rapidly than fir.

b. Application Rate: Despite the fact that the rate is the same: Arkansas has a broader spectrum of target species to deal with that is, 2,4,5-T is applied at an average of 2-3 lbs per acre.

c. Size of Treatment Unit: Cutting units in Arkansas range from 10-1000 acres, with an average of 200-500 acres. The average cutting unit in the Oregon national forests is on the order of 40 acres. This may suggest that the Arkansas population is at risk of exposure from fewer treatment sites than the Oregon population.

d. Topography: The commercial timber area in Arkansas consists of gently rolling hills rather than the steep slopes and narrow valleys of Oregon. This would seem to reduce somewhat the potential for drift. A network of streams like the one which runs through the Oregon forests does not exist. In Arkansas forests, the water supply comes from wells sunk over 1000 feet down. Hence, contamination of water supply is less likely.

e. Population Density: In comparison to the Pacific Northwest, the less rugged terrain of the Arkansas Plains produces a higher population density, as sample data indicate, and a more even distribution of population throughout the forested area.

f. Extent of Annual Treatments: In both Oregon and Arkansas, owners of timberland claim to treat 2-4% of their acreage per year.

g. Land Ownership: Commercial timberlands in Arkansas are entirely privately owned, mostly by a few large corporations. There are two national forests in the northwestern half of the state but they are hardwood, not pine producers, and thus do not use much 2,4,5-T.

In summary, although conditions in the Oregon forests may lead to a higher dose level of exposure, the Arkansas forests seem to have a larger population at risk of exposure.

h. Exposure records: The state of Arkansas regulates the use of 2,4,5-T, 2,4-D, and other hormonal herbicides, and requires that records of every application be filed with the State Plant Board. Private applicators, however, are exempted from this regulation. Most corporate timber operations have their own helicopters and hence qualify as "private" rather than "public" applicators. Thus, Plant Board regarding applications of 2,4,5-T on timber are substantially incomplete.

The corporate owners, who are banded together into a consortium called the Arkansas Forestry Association, keep their own records. If the study design met their approval and confidentiality of data was guarded, it would probably be possible to arrange to abstract their records. The proposed concomitant assessment of effects of use in the adjacent rice area was viewed as a strength of the study design by the local timber representative with whom we spoke.

2. Rice

a. Application and Acreage: The agricultural section of Arkansas is essentially the southeast portion of the state, particularly the region known as the Delta, located between the Arkansas and Mississippi Rivers. The principal crops are rice, soybean and cotton. The trend over time has been to increase the total acreage cropped, with a shift away from cotton to rice and soybean.

Currently the total acreage harvested in rice is about 1.2 million, with the two sample counties having the largest number of rice acres: in 1978, 114,000 acres of rice were planted in county C and in county D, 89,000 acres were planted in rice.

The use of 2,4,5-T in connection with rice cultivation has been described on pages 9-10 of this report. There it was noted that rice is typically alternated with soybean to restore the soil. Like cotton, soybeans are sensitive to 2,4,5-T; however, a number of other pesticides are recommended for use on cotton and soybean. In fact, pesticides other than 2,4,5-T are also applied to rice fields. Thus, the agricultural population is at risk of exposure to many chemicals. The table which follows lists all pesticides that may be used on rice, cotton or soybean. It is not possible to state with certainty that these other agents are without risk to human reproduction.

Table 4
Pesticides Recommended for Use on Rice, Soybean and Cotton

<u>Recommended Pesticides</u>	<u>Rice</u>	<u>Soybean</u>	<u>Cotton</u>
	Ordram	Basalin	Basalin
	Modown	Tolban	Cobex
	Propanil	Treflan	Prowl
	Ronstar & Pronpanil	Cobex	Tolban
	Propanil 3 & 3	Prowl	Treflan
	Propanil & Ordram 3	Lasso	Tolban & Cotoran
	Ordram 10 G	Lorox	Treflan & Cotoran
	2,4,5-T	Sencor-Lexone	Bladex 80 W

HERBICIDES	2,4,5-T & Propanil	Treflan or Tolban & Sencor-Lexone	Bladex 4L
	Silvex	Prowl & Sencor-Lexone	Cotoran or Lanex 80 W
	Basagran	Lasso & Senco or Lexone	Karmex or Dynex 80 W
	Basagran & Propanil	Treflan & Vernam 7E	Zorial 80 W
	Propanil	Lasso & Lorex	
		Lasso & Sencor Lexone	
		Surflan & Lorex	
		Surflan & Sencor-Lexone	
FUNGICIDES	Arastan 70%	Arasan	Basan 30
	Busan 30-A	Captan	Busan 30 & Demosan
	Captan	Terra-Coat L-205	Demosan-Thiram
	Difolatan	Vitavax -200	Dexon Daconil (72%)
	Dithane M-45	Terraclor Super X 10-2.5D	PCNB & Dexon
	Terra-Coat L-205	Benlate	Terra-Coat L-21
	Vitavax	Mertect 340-F	Terra-Coat L-205
	Benlate 50%		Vitavax & Captan
			Vitavax & Thiram
			Demosan D
			Demosan G
			Terraclor Super XG
			Terraclor Super XD
			Terraclor Super XE
			PCNB & Captan 30D
			PCND & Manab D
			PCNB-& Thiram D
INSECTICIDES	Metalkamate	Acephate	Acephate
	Carbofuran	Carbaryl	Aldicarb
	Malathion	Methomyl	Azinphosmethyl
	Methyl Parathion	Methyl Parathion	Carbaryl
	Carbaryl	Toxaphene	Chlorpyrifos
	Toxaphene		Chlordineform
			Propargite
			Dicrotophos
			Dimethosate
			Disulfoton
			Endrin
			EPN
			Fenraterate
			Malathion
			Methidiathion
			Methomyl
			Methyl Parathion
			Methyl Parathion FM
			Methamidophos
			Monocrotophos
			Permethrin
			Phorate
			Sulprofos
			Toxaphene
			Trichlorfon

Because susceptible crops are often contiguous to rice paddies, applicators attempt to control drift. Nevertheless, since many dwelling units are in or adjacent the fields and crops extend right to the edge of the towns and along both sides of the roads, there is clearly potential for human exposure associated with spray applications, even for individuals living on the edge of town.

Since this use of 2,4,5-T was not part of the EPA suspension process, 2,4,5-T will again be applied in Arkansas rice fields this coming summer. However, only half as much 2,4,5-T will be available for use as in the past because of declining stocks; manufacturers have ceased producing 2,4,5-T amine until after the current court action (involving a possible total ban on use of 2,4,5-T) has been settled.

b. Records of Exposure: As mentioned above, Arkansas requires that commercial applicators file both a notice of intent to apply the herbicide and a record of each application, containing information on the client; time and location of treatment (including distance and direction from nearest town); wind and air conditions; amount and composition of chemical used; crop treated; equipment used; and distance from susceptible crops.

These records are kept on file at the State Plant Board for a minimum of three years and are available for public scrutiny. The Plant Board considers its records to be quite complete with respect to agricultural use of 2,4,5-T.

3. Summary

The following factors are noteworthy in considering Arkansas as a site for studying exposure of 2,4,5-T in connection with applications on timber and rice:

Timber: Arkansas provides a larger population at risk of exposure to 2,4,5-T through timber use than does Oregon because commercial timber production extends over a larger area and the topography is more conducive to settlement.

Rice: The major issues to be considered in studying the effect of 2,4,5-T in agricultural settings are: (1) Exposure to 2,4,5-T is accompanied by exposure to many other chemicals, none of which have been systematically examined in relation to reproductive outcome; this is similar to the problem of multiple exposures that is frequently encountered in studying occupational cohorts. Thus, isolation of the effects of 2,4,5-T from effects of other exposures may be difficult. (2) Populations living near rice fields may be exposed to 2,4,5-T once or twice every three years. Therefore, a study in this setting offers the opportunity (and difficulty) to distinguish the effects of lifetime low-dose exposure from those of sporadic higher-dose exposure.

A great advantage of studying the rice setting is that there is continued use; thus, cross-sectional or prospective research designs could be considered.

Population At Risk Of Exposure

Two main factors emerge as important in considering the Arkansas population as a potential study group. First, it appears that sides have not formed nor have attitudes hardened on the issue of whether pesticides have adverse health effects. Certainly there is not the local furor in Arkansas

that exists on the West Coast and, presumably, not the same threat of reporting bias in this largely unresearched population.

Second, the population at risk of exposure to 2,4,5-T in Arkansas is, as on the West Coast forests, distinctive. In Oregon, the purported lifestyle of the forest residents is thought to relate to reproductive risk. In Arkansas the location of herbicide applications coincides with the location of a high risk obstetric population.

Among the poorest states in the nation, Arkansas has an excess of adverse pregnancy outcomes. The state's perinatal mortality rate of 20.8/1000 is similar to that of New York City. Its maternal mortality rate is double the national rate (22/100,000 livebirths v. 11/100,000). Its rate of teenage pregnancy may be the highest in the United States.

Within the state, indicators such as infant mortality, teenage pregnancy, and low birthweight show that the population with the worst reproductive outcome clusters in the southern part of the state; if one draws a diagonal line from Polk County in the southwest through Little Rock at the center of the state and up to Mississippi County on the eastern border, one finds that counties falling below the diagonal rank poorly on these indicators. This area also represents the site of 2,4,5-T use within the state. Thus, a high-risk population comprised of women with diabetes, hypertension, cardiac problems and other obstetric risk factors, is also the population at risk of exposure to 2,4,5-T.

Because the type of exposure in rice and in timber areas is different, we attempted to discover whether the two populations differed. Discussions with sociologists and anthropologists at the University of Arkansas, and with others knowledgeable about the state, suggest that they are fairly similar. Socioeconomically, the Delta and Plains areas (i.e., rice and timber areas, respectively, are similarly stratified, with timber companies and plantations functioning in analogous ways to produce communities where wealth and poverty coexist. Racially, there may be slightly fewer blacks in the Plains than in the Delta.

C. Reproductive Outcome Data

The medical care systems for rich and poor are separate. In addition, prenatal care and care for delivery are also frequently separated, with women receiving prenatal care locally but traveling to population centers to deliver.

1. Public Patients: The separation of place of prenatal care from place of delivery occurs largely with poor patients, who typically deliver at the one indigent care center in the state, located in Little Rock. Prenatal care for the poor, including pregnancy testing, is offered through local Health Department clinics. Two and a half years ago, the state set up a fairly extensive prenatal care system throughout the rural areas, using a cadre of nurse practitioners specially trained in maternity care. Although poorer patients typically come in rather late (after the first trimester), the Health Department follows them closely and keeps a log of their progress on file. Patients reporting a spontaneous abortion are referred to Little Rock or to general practitioners for care.

Until recently, there was a widespread network of granny midwives operating in the rural areas, but the state has tried to eliminate this type of care.

2. Private Patients:

Private patients receive their obstetric care either from OB/GYN specialists located in the urban areas, or from family practitioners. Specialist obstetric care is at a premium in the state, and private patients often wait 2 to 3 months to see an obstetrician. (In fact, the Health Department has begun to offer interim services to such patients.) Some of the physicians we have interviewed expressed reluctance about having their records utilized in research, because of their concern regarding the confidentiality of the patient/chart or because such research might disrupt the already busy office. The Health Deptmt expressed willingness to share their records with us, and several hospitals offered use of their premises for our research.

3. Summary: The following factors emerge as relevant to a study of reproductive outcome in Arkansas:

- (a) Difficulty in finding obstetric data on local women;
 - (b) Incomplete data on reproductive events in medical records;
- and
- (c) Prerequisites for access to medical records.

(a) Tracing obstetric events of local women: Because of the organization of obstetric services, women from the same area may seek care from a number of different sources at a considerable distance from home. Conversely, the same practitioner may deliver care to women from many different areas. Thus, the use of records to ascertain the reproductive events of a certain local population would be difficult and inefficient.

(b) Incomplete data on reproductive events: There may be a considerable underestimate in medical records of reproductive events, especially of early fetal loss, and especially those occurring to the poor. Poor patients come for care quite late in pregnancy, later on average than when most spontaneous abortions occur. Also, because prenatal services for the poor are a fairly recent development, some women may continue to rely on midwives or self-care. Opinion varies as to the extent of loss these factors produce.

(c) Prerequisites for access to medical records: For those reproductive outcomes which are reported in the medical records, it may be necessary to obtain prior consent from the patient to review the medical chart.

D. Development of a Study Design in Arkansas: In Arkansas, as in Oregon, the research design for studying the relationship of 2,4,5-T to reproductive outcome must evolve from both the hypotheses to be tested and the characteristics of the study population. We discuss each in turn, concluding with a description of the approach suggested by the nature of the site; an estimate of the size of the sample available for study; and a summary and recommendations.

1. Hypothesis to Be Tested: The use of Arkansas rather than Oregon as the site for study allows the test of a more comprehensive set of hypo-

theses. Three types of exposure could be investigated. In the timbered area, the population is at risk of a relatively high-dose exposure occurring very occasionally over a lifetime. Thus this population permits one to examine the effects of a single intense exposure to 2,4,5-T. The residents of the rice areas are at risk of a low-dose exposure which occurs repeatedly over a lifetime. In this population, one could examine two types of effects: the effects of acute, low-dose exposure; and the effects of chronic and possibly accumulating exposure. Thus, Arkansas provides a setting in which to study the relationship of pregnancy outcome to 2,4,5-T exposure which occurs either long before conception or immediately prior to conception, as well as during pregnancy. It is therefore possible to consider whether exposures in childhood or the very early reproductive years have an impact on the outcome of later, unexposed pregnancies.

2. Factors Affecting Study Design Decisions: Characteristics of the types of exposure, the data and the study population have been alluded to in the preceding text but are set out systematically in the following table. Next to each condition mentioned, we specify a research strategy which may answer the problem posed by the condition. A discussion of the strengths, limitations and unresolved issues associated with the various study design options follow the table.

Table 5

ARKANSAS: Conditions Affecting Study Design

<u>Conditions</u>	<u>Design Decision</u>
1. A continuing, as well as suspended, herbicide use available for study.	Cross-sectional, prospective, or retrospective approaches could be taken.
2. Incomplete and inaccessible medical records.	Interviews with residents rather than records as the primary source of data.
3. No evidence of potential bias in reporting by residents.	
4. Population at risk has high-risk obstetric profile.	Restrict analysis to comparisons within the same population.
5. Possible cumulative effects from chronic agricultural exposure.	Compare with a population never exposed to 2,4,5-T.
6. Problem of multiple exposures of farm population.	Compare to population with similar exposures but not to 2,4,5-T, or establish effect first, disentangle later.
7. Low prevalence of exposure in timbered areas.	Select samples depending on treatment status during the study years of interest.
8. Seasonality of exposure.	Control for time of conception.
9. Different periods at risk of exposure for spontaneous abortions and livebirths.	Control length of gestation to equalize period at risk.

a. Discussions of Study Design Options

1. Possible Cross-sectional and/or Prospective Data Collection:

Be-cause the use of 2,4,5-T in agriculture is continuing, albeit on a limited basis, it may be possible to collect at least some of the data on exposure and pregnancy outcome either cross-sectionally or prospectively. The use of systematic drift and residue data would permit development of a better index of individual exposure. With respect to spontaneous abortion, it would be advantageous to arrange to examine the abortuses since such an examination would add specificity to the description of the outcome (e.g. chromosomally normal conceptus or abnormal conceptus with specific anomalies, or abortus with morphologic abnormalities). Concurrent measures of both exposure and outcome would certainly strengthen inferences regarding an association between the use of 2,4,5-T and poor pregnancy outcome.

There is at least one facility in a rice growing county where a hospital-based study of spontaneous abortions might be set up. The number of women treated for spontaneous abortion in this hospital is not large (N 150 annually), and thus a cross-sectional study limited to this setting would be inadequate to test the hypothesis that exposure has a modest effect on the frequency and nature of spontaneous abortion.

If, however, the effect of 2,4,5-T is to induce chromosomal or morphologic anomalies which are ordinarily rare, then a comparison of the chromosomal and morphologic data from this hospital with the data we have obtained in our New York City study should point up this effect. Thus, depending on the costs involved in carrying out such a study, it may be a valuable adjunct to a larger investigation based on historical data about previous pregnancy outcomes.

Given that 2,4,5-T is no longer used in the timber area, a retrospective analysis essentially identical to that described for Oregon is proposed. We consider it likely that a similar analytic approach would be taken in the rice areas. A major difference, however, between the Oregon and Arkansas studies is in the source of the data on previous obstetric events: record review in Oregon and personal interview in Arkansas.

2-3. Source of Data on Pregnancies: For the reasons cited in Table 5 and described above, the preferred approach to identifying pregnancies appears to be through personal interviews with residents rather than a search of medical records. Ordinarily, interview data generate a more complete account of reproductive events than other methods, although it may not be possible to confirm all information. An attempt could be made, however, to validate the reproductive outcomes for which care was sought at a medical facility or from midwives and to evaluate the reliability of reports through interviews with husbands, friends or relatives. Unvalidated and validated outcomes could also be analyzed separately, and the results of these analyses compared.

In addition to a more complete obstetric history, interviews with residents provide an opportunity to develop supplementary data on other sources of exposure and on potentially confounding variables.

It is not clear at this time how the sample to be interviewed would best be selected and approached. A further feasibility study is needed to determine: (1) whether sample selection should be based in health care institutions, other institutions (e.g. church groups) or in entire communities; (2) whether residents will willingly discuss their reproductive history; (3) whether the racial or regional characteristic of the interviewer will influence the quality of the interview data (opinions of local sociologists and anthropologists vary on this question); (4) whether the respondents can provide valid reliable and detailed data on previous pregnancies.

4. Obstetric Risk Factors: The fact that the use of 2,4,5-T within Arkansas coincides with the location of a high risk obstetric population is similar to the problem faced in Oregon in regard to the lifestyle of the forest residents, and can be dealt with similarly. That is, the possibility of confounding by such risk factors may be limited by restricting data collection to homogeneous populations, within which some members are exposed and others are not exposed to 2,4,5-T. Potentially confounding variables may be controlled statistically in the analysis.

5. Lifetime Risk: In order to test whether there are effects associated with chronic, but not current, exposure to 2,4,5-T, the comparison population must necessarily be one that has never been exposed to 2,4,5-T. It seems likely that the timbered area of the state, where exposure occurs so infrequently, should generate a suitable control group for the residents of the rice-growing areas who have been exposed in the past but not in relation to their current pregnancy. A comparison between these two groups, who are said to be similar in other relevant respects, should provide a test of "ever"/ "never" exposure.

A nonpositive finding from such a comparison would provide convincing evidence that chronic exposure to 2,4,5-T is without long-term effects. A positive association, however, would not implicate 2,4,5-T alone since individuals chronically exposed to this herbicide are also chronically exposed to a wide range of other pesticides. In the event of a positive association, data on a population exposed to similar agents, excepting 2,4,5-T, would be needed to determine whether exposure to 2,4,5-T was the relevant factor. Perhaps the population in the Texas rice fields, where MCPA is used in lieu of 2,4,5-T, might provide suitable controls. In view of the difficulty and expense involved in carrying out the proposed study, it seems most practical to attempt at the start to establish that an effect exists in association with agricultural herbicide use, and defer the problems of targeting the specific agent responsible.

6. Concomitant Exposures: The multiple chemical exposures sustained by Arkansas' agricultural population pose less of a problem in evaluating the effects of acute exposure in the agricultural setting. Within any one year, 50-60% of the population is exposed to 2,4,5-T. Exposed and unexposed individuals are similar in terms of their lifetime exposure to 2,4,5-T and other chemicals. Within any one year, however,

the other chemical exposures of individuals exposed to 2,4,5-T may differ from those of individuals not exposed to 2,4,5-T. It is apparent that there is a marked overlap in insecticides and fungicides used in rice and soybean farming (see Table 4, pp 34. Thus, any difference in exposure to other chemicals between residents living near rice (exposed to 2,4,5-T) and soybean (not exposed to 2,4,5-T) crops may be limited to one or a few specific herbicides. If the application times for these different herbicides vary, it may well be possible to disentangle the effects of 2,4,5-T from those of other exposures encountered during the same season. Insofar as the findings on acute exposure are similar in the rice and timber areas, the inference that an association in the rice area is linked to 2,4,5-T, rather than to other chemicals, will be strengthened.

7. Sampling Procedures: Since timber use of 2,4,5-T covers a great expanse of Arkansas, it would be most efficient to select the study samples depending on treatment status during the years for which spray data are available. By consulting records of past herbicide applications, it should be possible to target areas known to have been treated during the relevant years, thus making the population selected for study as informative as possible.

8-9. Seasonality/Length of Period at Risk: The seasonality of 2,4,5-T use and the problem of livebirths and spontaneous abortions being at risk of exposure for different durations of gestation are the same problems as were raised and discussed in connection with the Oregon study, and can be hand-led similarly here; that is, by matching pregnancies ending in abortion and term pregnancies for time of conception and by curtailing the period used to define exposure in term pregnancies.

b. Estimates of Sample Size

The number of cases of spontaneous abortions and of term births (controls) occurring per year in both the 18 counties where timber is grown commercially and the 13 counties which have substantial acreage planted in rice have been estimated. As was described in the section on sample size determinations for Oregon, the expected number of spontaneous abortions was derived by considering the number of livebirths, from published vital statistics, to represent 85% of pregnancies. (The expected rate of abortion is estimated at 15% of recognized conceptions.) We consider that at least 80% of women will consent to be interviewed and thus 80% of abortions will be identified. The numbers set out below represent the estimated numbers of spontaneous abortions and term births for one year. The length of the study period has not been determined; however, the State Plant Board keeps records for a minimum of three years, and so an upper limit of three years of pregnancies is available.

Although the two exposed areas generate similar numbers of abortions per year, one might need study periods of differing lengths in the timber and the rice areas. Given that the prevalence of exposure is so

different in the two populations, the power provided by samples of the same size will vary. Thus the low frequency of exposure in forested areas requires that a larger sample of pregnancies be studied to test for a modest effect.

It should also be noted, however, that the forested areas of Arkansas provide more cases in one year than could be garnered in Oregon over five years ($N = 742$ per year in Arkansas, v. $N = 600$ per 5 years in Oregon.)

Sample Sizes Available

- 18 Timber Counties: 5,255 births and an estimated 742 spontaneous abortions per year.
- 13 Rice Counties: 5,450 births and an estimated 769 spontaneous abortions per year.

In summary, it appears that Arkansas may provide a suitable site in which to examine the relation of 2,4,5-T exposure to spontaneous abortions.

VIII. Summary and Recommendations

We have reviewed several issues bearing on the decision to examine the relation of 2,4,5-T exposure to spontaneous abortion. Two sites have been considered: the Pacific Northwest where 2,4,5-T is applied to timber, and Arkansas where 2,4,5-T is applied both to timber and rice fields. The primary strategy proposed to study this relation is similar for both sites. We propose that the frequency of exposure to 2,4,5-T be compared among women experiencing spontaneous abortions (cases) and women delivering after 28 weeks gestation (controls). Controls would be matched to cases for month of last menstrual period and maternal age. Exposure status for controls would be assigned only for that period which corresponds to the gestation of the matched case at the time of spontaneous abortion.

Apart from the similarity in the analytic approaches which would be taken to study the relation of 2,4,5-T exposure to spontaneous abortion in either setting (the Pacific Northwest or Arkansas), there are differences in the range of hypotheses which may be tested, the source of data and the sample sizes available, which bear on the choice of a study setting. Each of these is discussed below.

1. Range of Hypotheses

The hypotheses which may be tested differ depending on whether the herbicide use is for timber or rice production. In the timber areas in the Pacific Northwest and in Arkansas, previous exposures to 2,4,5-T were infrequent, brief and possibly of fairly high dose. Therefore, in either of these areas, the test would be of the relation of an acute exposure, either prior to or during pregnancy, to spontaneous abortion. Although it is possible that contamination of food and water supplies may follow spraying and provide a possible chronic exposure, this route

of continued exposure has not been broadly demonstrated. Indeed, the observation which drew attention to the possibility that 2,4,5-T exposure is related to abortion suggests that an effect, if present, coincides with the time of spraying. We consider, therefore, that the hypothesis best tested in a timber area is that acute, rather than chronic, exposure is associated with spontaneous abortion.

In the rice areas in Arkansas it is possible to examine the relation of both acute and chronic 2,4,5-T exposure to spontaneous abortion. In each year, approximately 50-60% of the acreage is planted with rice, and it is a fair inference that approximately the same proportion of the population may be exposed.

In the agricultural setting numerous pesticides are used, making it difficult to isolate the effects of 2,4,5-T. Nevertheless, because rice is alternated with broadleaf plants, there will be a segment of the population in any year that is not exposed to 2,4,5-T. Thus enabling a comparison between reproductive experience in a group currently exposed and a group currently unexposed to 2,4,5-T will be possible. This approach is similar to the one frequently employed in occupational studies: the exposed workers are often compared to a group of workers from the same industry who are exposed to chemicals other than the agent under study.

A study which examines the effects of both timber and agricultural use has the advantage that the effects of acute exposure associated with these two uses may be compared. If the findings from the rice area are similar to those from the timber area, where the population is not exposed to multiple pesticides, the inference that 2,4,5-T, rather than some other pesticide, is associated with abortion will be strengthened. Since the fields sprayed with 2,4,5-T may also be treated with other herbicides not used in areas which are not sprayed with 2,4,5-T, the finding of an association of 2,4,5-T exposure with abortion in the rice areas but not in the timber area will be difficult to interpret. It may be possible to distinguish the effects of 2,4,5-T from other herbicides (on which data will also be collected) if the effect of 2,4,5-T is limited to a short time interval, either during gestation or immediately prior to conception.

In Arkansas it is also possible to examine whether long-term residence in a rice-growing community is associated with spontaneous abortion by comparing the rates of spontaneous abortion in the rice counties with that in the timber counties. The failure to detect an association will suggest that chronic exposure to 2,4,5-T is not associated with spontaneous abortion. A possible association between residence in the rice area and spontaneous abortion would not specifically implicate 2,4,5-T because of the concomitant exposures to other pesticides. As mentioned earlier, in the event of a positive association, it would be necessary to collect data from another rice-growing area in which 2,4,5-T is not used in order to determine whether the observed effect is owed to exposure to this pesticide alone.

2. Sources of Data

The data source differs depending on the location (Pacific Northwest or Arkansas) of the study. In the Pacific Northwest, physician records would serve as the data source for information on pregnancy outcomes. This data source is unlikely to be affected by the current debate regarding the merits of pesticide use. This debate would probably affect the quality of interview data. A strength of record-based data is that it will be possible to distinguish spontaneous abortions where pregnancy was confirmed either by a pregnancy test or pathologic examination of the abortus, from those where it was not. There are, however, several limitations to using this data source: (1) for some spontaneous abortions which were known to the physician at the time of abortion there will not be sufficient data in the record to permit use in the analysis; (2) pregnancies where medical attention was not sought will not be included in these records; (3) data on potentially confounding variables (e.g. smoking) will not be available. It is not possible to estimate the way in which these limitations may affect the results; this depends in part on whether there is an association between exposure and the use of medical facilities for care of a spontaneous abortion. Such an association would arise, for example, if exposure leads to early spontaneous abortions and a low proportion of women experiencing early abortions (e.g. 40%) attend physicians. In this example, the association of exposure with abortion may be missed.

In Arkansas, data on previous obstetric events would be collected by interview with women. This method of data collection ensures more complete information on all three types of variables: pregnancy outcomes, including exposure through occupation and home and garden use of pesticides; and potentially confounding variables. A limitation in using this method of data collection in this setting is that it may not be possible to validate all reports of pregnancy outcomes.

Frequently the limitations of record-based data are offset by the ease with which they are collected. This is not the case, however, in the Pacific Northwest, where it will be necessary to abstract the obstetric records of all physicians practicing in the area.

While the proposed interview study in Arkansas will also entail an extensive effort, the data obtained in this study will be far more comprehensive than those obtained in the record review study. In regard to the exposure variable, in the Arkansas study it will be possible to gather information on residence both prior to and during pregnancy (i.e. whether vacations were taken) and whether there may have been other routes of exposure. Furthermore, in the rice areas, data on the drift of spray and residue in foods could be collected during the spraying season.

3. Sample Size

The population available for study in the Pacific Northwest is small. In order to develop a sample of reproductive events of sufficient size to insure that the study will have adequate power to detect

a moderate effect (odds ratio =2), both the Oregon and Northern California regions must be studied. Conducting a study over a large area (and across state lines) may have implications for both cost and efficiency, since exposure data would need to be obtained from several sources. Furthermore, exposure and reproductive data extending over a five-year period (1973-78) would be needed; and the quality of these data may vary with study year.

In Arkansas a considerably larger population is at risk of exposure. For example, in a single year, the forest area of this state can generate more cases of spontaneous abortions than are expected in the Oregon forest over a five-year period. The larger the sample, the greater the power of the study to detect modest effects.

The large population available for study in Arkansas also has the advantage that only one pregnancy for each couple would need to be used in the central analysis, although data on all pregnancies to each couple will be collected. In the power calculations presented earlier for the Pacific Northwest, we have permitted more than one pregnancy per couple to enter the analysis. We have not yet resolved whether this approach is consistent with the assumption that observations must be independent in order for a contingency table analysis of the type proposed here to be appropriate. If, on further consideration of this issue, we determine that the assumption of independence requires that only one pregnancy per couple enter the analysis, then the power of the Pacific Northwest study is even lower than that set out previously. A similar problem does not arise for the Arkansas study, where, if needed, there are sufficient numbers of couples to provide the needed numbers of single reproductive events.

In sum, we consider that the Arkansas timber and rice areas are likely to permit a more thorough examination of the relation of 2,4,5-T exposure to spontaneous abortion than the Pacific Northwest timber areas. Arkansas offers strong advantages both in the range of hypotheses to be tested, the quality of the reproductive and exposure data, and the size of effects which may be detected with adequate statistical power. We have not yet evaluated the feasibility of collecting data by interview in this region, and so a firm conclusion regarding the potential of this site for the proposed study awaits this assessment.

4. Summary

A study carried out in the Pacific Northwest coastal region would provide an ecologic test of the hypothesis that 2,4,5-T exposure is associated with spontaneous abortion. Given that the data would be confined to obstetric events recorded in physician records (possibly about 50% of all recognized abortions) and that proximity of any individual to spray application site can not be confirmed, the results will be limited in their implications for a casual relation between 2,4,5-T exposure and spontaneous abortion. If both the obstetric and spray data were already computerized and available for linkage, it would be efficient and expedient to carry out the proposed ecologic analysis. However, given that these data must be abstracted in order to carry out this analysis, the costs of such data collection must be weighed against

the limited hypotheses and inferences which attend an ecologic study in this small population.

In contrast, Arkansas provides a setting in which the relation between 2,4,5-T and spontaneous abortion might be examined on an individual level. The effects of both chronic and sporadic exposure may be examined in this state where two major types of herbicide use are found in adjacent areas.

Appendix A
Reproductive Outcome Data

A. PHYSICIAN INTERVIEWS

Name _____

Address _____

Phone _____

Time and date of interview _____

For physicians practicing in a group, please note:

number of physicians in the practice _____

whether procedures and record are uniform _____

Period over which the office has done obstetrics: _____

1. Ask for an estimate of the following data by month or by year, whichever the interviewee finds easier: (For group practices, get totals for the group, not just for the physician interviewed.)

total deliveries: _____

total spontaneous abortions: _____

seen in office _____

telephone report only _____

total spontaneous abortions hospitalized by this office: _____

at what hospital(s) _____

2. What proportion of obstetric cases in (name the area of interest) does this office handle?

3. Characteristics of obstetric population:

- (a) patient residence
- (b) race
- (c) education
- (d) age
- (e) other demographic characteristics

4. Ask for estimate of the proportion of women in (name area of interest) with (a) livebirths and (b) spontaneous abortions who do not attend a hospital, physician, or other medical facility for care. (We need to gauge what proportion of reproductive events could not be either ascertained or validated in physician or hospital records.)

4a. What is the basis for this estimate?

5. How soon after their last menstrual period do patients usually come in for confirmation of pregnancy? (NOTE: IF physician gives a broad range, ask what percent comes in at the early end and what proportion towards the end of the range. The purpose of the question is to find out how many first trimester abortions may not be medically attended.)

5a. What proportion are confirmed by pregnancy test? What proportion by physician exam?

5b. Where pregnancy tests have been used, ascertain:

type of pregnancy test _____

where results are analyzed _____

where results are recorded _____

6. What proportion of patients experiencing spontaneous abortion have had their pregnancy confirmed before the abortion?

6a. Of that proportion, how many by pregnancy tests? how many by PE?

7. What is the office protocol with respect to a spontaneous abortion when:

- (a) patient gives self-report by phone, pregnancy unconfirmed prior to phone call.
- (b) patient phones in self-report, pregnancy has been confirmed prior to phone call.

Is the phone contact recorded in the chart? Is date of abortion recorded? Is LMP recorded? What other data are recorded?

Is a patient visit always or sometimes required following report of spontaneous abortion?

What proportion of patients reporting spontaneous abortion are hospitalized? and for what reasons?

Are pathologic examinations done on the products of conception to confirm pregnancy? When and where?

Pregnancy unconfirmed:

Pregnancy confirmed

8. Hand the interviewee the sheet with the list of variables (checklist of variables) and have him/her fill out.

9. How many total charts does this office have? _____

How are they filed and stored? _____

10. In this office, is there any way to pull only those charts of women who have had pregnancies -- e.g., an ongoing list of OB patients; list of those pregnancy tested; list of path exams on POC; etc.

11. Within the chart, is there any quick way to retrieve all data on pregnancies?

12. Would he/she agree to a record search if a study were to be undertaken?

13. Ask whether doctor would be willing to provide us access to names of patients for the purpose of linking across facilities. (We would of course respect confidentiality of patients.)

14. Is amniocentesis available to patients? If so, where, and for what reasons?

15. FOR ALL INTERVIEWEES: Ask to review 2-5 randomly selected charts.
(In case of a group practice, ask for two charts per physician.)
- (a) check especially for information on smoking, alcohol, residence, occupation.
 - (b) note whether chart:
 - i. is typed or handwritten; if latter, is it legible?
 - ii. does or does not have a facesheet?
 - iii. is organized from current to past, or vice versa?
 - iv. provides a continuous history or has separate chart for each calendar year?
 - (c) in case of GP, is reproductive data difficult to cull from record?

Comments:

Appendix B

Checklist of Variables

Interviewee _____

Address _____

Phone _____

For the following variables, please estimate what proportion of your records contain this information:

a) for a live or still birth

b) for a spontaneous abortion

_____	DATE OF LMP	_____
_____	DATE OF ABORTION OF BIRTH	_____
_____	OTHER ESTIMATES OF GESTATION (e.g. intrauterine size)	_____
_____	MOTHER'S DATE OF BIRTH	_____
_____	FATHER'S DATE OF BIRTH	_____
_____	MOTHER'S PREVIOUS REPRODUC- TIVE HISTORY	_____
_____	RACE OF MOTHER	_____
_____	RACE OF FATHER	_____
_____	EDUCATION OF MOTHER	_____
_____	EDUCATION OF FATHER	_____
_____	OCCUPATION OF FATHER	_____
_____	OCCUPATION OF MOTHER	_____
_____	PREGNANCY TEST RESULTS	_____
_____	PATHOLOGICAL REPORT ON PRODUCT OF ABORTION	_____
_____	ZIP CODE OR OTHER INDICATOR OF PATIENT ADDRESS	_____

_____	MATERNAL SMOKING	_____
_____	MATERNAL ALCOHOL CONSUMPTION	_____
_____	MATERNAL IRRADIATION EXPOSURES	_____
_____	MATERNAL VIRAL INFECTION	_____
_____	SEX OF LIVEBIRTH	
_____	BIRTHWEIGHT OF LIVEBIRTH	
_____	CONGENITAL MALFORMATION IN LIVEBIRTH	
_____	CONGENITAL MALFORMATION IN STILLBIRTH	

Appendix C

Reproductive Outcome Data

B. HOSPITAL INTERVIEWS

Name _____

Address _____

Phone _____

Time and date of interview _____

Name of Hospital _____

Number of beds total _____

Number of OB beds _____

Number of physicians admitting OB/Gyn patients _____

1. Ask for an estimate of the following data by month or year, whichever the interviewee finds easier:

total deliveries: _____

total spontaneous abortions: _____

Inpatients _____

Outpatients _____

Clinics _____

ER _____

total induced abortions: _____

2. Does this hospital have a 'Birth Registrar' - someone who keeps summary data on births, stillbirths, induced and spontaneous abortions?

3. Are fetal death certificates filled out in hospital? Beginning at what gestation?

4. Please characterize your OB population in terms of:

- (a) residence
- (b) race
- (c) education
- (d) age
- (e) other demographic characteristics

5. Please estimate the proportion of women in the area with (a) livebirths and (b) spontaneous abortions who do not attend a hospital, go to a physician, or other facility for care. (We need to gauge what proportion of reproductivity events could not be either ascertained or validated in physician or hospital records.)

5a. What is the basis for this estimate?

6. Are most patients with livebirths or spontaneous abortions admitted through a private physician, or do some patients have no physician?

7. a. How are charts filed - by name, unit number, admitting or discharge diagnosis? It is possible to access charts by diagnosis?

b. Are the records computerized? If so, are outpatient records computerized as well?

c. What data are entered onto the computer?

8. How would one identify every spontaneous abortion that occurred at your hospital? IF RECORDS ARE COMPUTERIZED: Have you ever checked whether your computer records pick up every case from the admissions book, path. log, OB clinic log, etc.?
9. Hand the interviewee the sheet with the list of variables (checklist of variables) and have him/her fill out. In the interest of clarity, ask them to distinguish those data that are coded from those that appear in the chart only.

10. Ask for a printout, to take home, for several years' worth of both livebirths and spontaneous abortions, by zip code, maternal age, date of LMP, and date of event.
11. If we were to do a study could we have access to their records?
12. Could we have access to patient names for the purpose of linking across facilities?
13. Do they offer amniocentesis? If so, for what reason?